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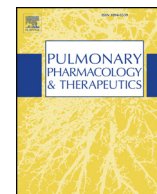
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# Impact of doxofylline in COPD: A pairwise meta-analysis

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## ABSTRACT

Doxofylline is an effective bronchodilator for relieving airway obstruction in patients with asthma or chronic obstructive pulmonary disease (COPD), and displays a better safety profile with respect to theophylline. Herein, we performed a pairwise meta-analysis of the currently available data to provide consistent and homogeneous findings on the impact of this xanthine in COPD patients. Results obtained from 820 patients were selected from 20 clinical trials. Meta-regression was performed to examine the source of heterogeneity between-studies and identify potential confounder covariates. The quality of the evidence was assessed by the GRADE system. Doxofylline induced a significant ( $P < 0.001$ ) increase in forced expiratory volume in 1 s ( $FEV_1$ ) of 8.20% (95%CI 4.00–12.41;  $I^2$  93%) and 317 ml (95%CI 19–439;  $I^2$  87%) compared with baseline. The total administered dose of doxofylline significantly ( $P < 0.001$ ) interacted with the size of the effect estimates detected for  $FEV_1$ . Doxofylline induced a significant ( $P < 0.001$ ), although moderate, increase in adverse events (AEs) frequency (proportion 0.03, 95%CI 0.02–0.04;  $I^2$  88%), but only epigastralgia, nausea, dyspepsia and headache were statistically significant ( $P < 0.05$ ). The GRADE analysis indicated high quality of evidence (+ + + +) for the impact of doxofylline on  $FEV_1$ , and moderate quality of evidence (+ + +) for the safety profile in COPD patients. Doxofylline is an effective and safe medicine when administered to patients with COPD and can be considered as an alternative to theophylline.

## 1. Introduction

Doxofylline is a xanthine that is structurally different from theophylline by having a dioxalane group at position 7 of the xanthine ring [1]. Consequently, it has mechanisms of action distinct from those of theophylline [2–4] in that lacks adenosine receptor antagonism or the ability to inhibit any of the known PDE isoforms, which may contribute to the better safety profile. Furthermore, unlike theophylline, doxofylline does not interact with histone deacetylases [3], but is able to positively interact with  $\beta_2$ -adrenoceptors [5].

The narrative analysis of literature has suggested that doxofylline is an effective bronchodilator for relieving airway obstruction in patients with asthma or chronic obstructive pulmonary disease (COPD) and displays a better safety profile with respect to theophylline, having a favourable risk-to-benefit ratio [2,4,6]. Unfortunately, narrative reviews primarily focused on the conclusions reached in various studies [7] and, furthermore, mainly related with the researchers' personal

preference. Therefore, in evaluating this type of research, one needs to examine how the critical analysis was done, ensuring the rigor in the methodology and the review process, and checking for possible bias stemming from the researchers' choices surrounding the development of the research aim/question, the selection of articles to review, and the transparency in their process or lack of it [8].

Meta-analysis, which is an analytical technique designed to summarize the results of multiple studies, represents a powerful way to effectively increase sample size to provide a more valid pooled estimate [9]. Meta-analysis can be considered as a systematic study of all studies that have been conducted to answer a specific question or hypothesis [10]. Actually, the meta-analytic approach usually has four main goals: (1) to evaluate the consistency/variability of the results between the primary studies included in the review (i.e., the between-study heterogeneity); (2) to investigate and explain (if feasible) the causes of any observed heterogeneity (e.g., through subgroup or meta-regression analyses) to improve scientific understanding; (3) to calculate a

**Abbreviations:** AE, adverse events; CI, confidence interval; COPD, chronic obstructive pulmonary disease;  $FEV_1$ , forced expiratory volume in 1 s; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MCID, minimal clinically important difference; MD, Mean Difference; MRC, Medical Research Council; PLN, Logarithmic transformed Proportion; Pr, proportion; RCTs, randomized clinical trials; SE, standard error; SMD, Standardized Mean Difference

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summary effect size along with a confidence interval; and (4) to assess the robustness of the cumulative effect size through sensitivity analyses and formal evaluations of the potential sources of study bias, including publication bias, that stem from the primary studies and might have an impact on the calculated summary effect [8].

We have therefore investigated the use of doxofylline in the treatment of patients with COPD patients using a pairwise meta-analysis of the currently available data in order to provide consistent and homogeneous findings.

## 2. Materials and methods

### 2.1. Search strategy

This pairwise meta-analysis has been registered in PROSPERO (registration number: CRD42017077901; available at [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=77901](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=77901)), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Figure S1) [11]. This quantitative synthesis satisfied all the recommended items reported by the PRISMA-P 2015 checklist [12].

We undertook a comprehensive literature search for published and unpublished clinical trials (both randomized and non-randomized) evaluating the influence of doxofylline in COPD patients. Observational studies were not included in this meta-analysis. The terms “doxofylline” and their synonyms (doxophylline, doxofilline, doxofillina) were searched for the drug, and the terms “chronic obstructive pulmonary disease” OR “COPD” were searched for the disease. The search was performed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Scopus, Google Scholar, Web of Science and ClinicalTrials.gov databases through September 2017, in order to provide for relevant studies available up to September 20, 2017. Studies reporting the impact of doxophylline vs. control (placebo, untreated subjects, baseline values) on lung function and safety in COPD patients were included in this meta-analysis.

Two reviewers independently checked the relevant studies identified from literature searches and databases. The studies were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

### 2.2. Quality score, risk of bias and evidence profile

The Jadad score, with a scale of 1–5 (score of 5 being the best quality), was used to assess the quality of the studies concerning the likelihood of biases related to randomization, double blinding, withdrawals and dropouts [13]. A Jadad score  $\geq 3$  was defined to identify high-quality studies. Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The risk of publication bias was assessed by applying the funnel plot and Egger's test through the following regression equation:  $SND = a + b \times \text{precision}$ , where SND represents the standard normal deviation (treatment effect divided by its standard error [SE]), and precision represents the reciprocal of the standard error. Evidence of asymmetry from Egger's test was considered to be significant at  $P < 0.1$ , and the graphical representation of 90% confidence bands are presented [13].

Meta-regression analysis was performed to examine the source of heterogeneity between studies and identify potential confounder covariates specifically for the primary endpoints [14].

The quality of the evidence obtained for the primary endpoints was assessed in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [15].

### 2.3. Data extraction

Data from included studies were extracted and checked for study

characteristics and duration, doses of doxofylline, concomitant medications, disease characteristics, ethnicity, age, gender, lung function, safety, and Jadad score.

### 2.4. End points

The primary endpoints of this meta-analysis were the impact of doxofylline vs. control in terms of changes in forced expiratory volume in 1 s (FEV<sub>1</sub>) and frequency of adverse events (AEs). The reported length of follow-up could not be the same across clinical trials. Considering that the probability of detecting an AE is proportional to the duration of treatment, in this meta-analysis data on AEs have been normalized as a function of events per person-time (namely person-week), in which the numerator represents the count of total AEs and the denominator represents the given time duration multiplied by the number of patients [16,17].

The secondary endpoints were the therapeutic efficacy (the rate of patients that achieved the 3<sup>rd</sup> or 4<sup>th</sup> rank in a four-point non-validated scale, or that achieved the 2<sup>nd</sup> or 3<sup>rd</sup> rank in a three-point non-validated scale, where the higher values represented greater therapeutic efficacy [18–22]), the daily use or rescue medication (short-acting  $\beta_2$ -agonists), and the assessment of dyspnea via Medical Research Council (MRC) scale [23], or a non-validated dyspnea score that assessed dyspnea with a 4-point scale [24,25]. More details concerning the scales used to assess the therapeutic efficacy and dyspnea are reported in the supplementary data file (Table S1).

### 2.5. Data analysis

Results are expressed as Standardized Mean Difference (SMD), Mean Difference (MD), Proportion (Pr), Logarithmic transformed Proportion (Log Proportion, PLN), and 95% confidence interval (95%CI). The overall changes in FEV<sub>1</sub> are reported as SMD ( $\text{SMD} = [\text{difference in mean outcome between groups}] / [\text{standard deviation of outcome among participants}]^{-1}$ ), since this outcome was not always described in a standard manner across the studies (sometimes expressed as % predicted instead of volume [L or ml]). SMD has been also re-expressed in agreement with the rules of thumb proposed by Cohen and The Cochrane Collaboration\* [17,26]. Specifically  $< 0.5$  represents a small effect, 0.5 to 0.8 a moderate effect, 0.8 to 1.3 a large effect, and  $> 1.3$  a very large effect. The subset analyses of the changes in FEV<sub>1</sub> specifically expressed as % or volume (L or ml) are reported as MD. The frequency of AEs and the therapeutic efficacy are reported as Pr since most studies (85%) compared doxofylline vs. active comparators and not vs. placebo. Data on symptoms (dyspnea scores) are reported as MD and the use of rescue medication as PLN.

Since data were selected from a series of studies performed by researchers operating independently, and a common effect size cannot be assumed, we used the random-effects model in order to balance the study weights and to adequately estimate the 95%CI of the mean distribution of drugs effect on the investigated variables [27].

Subset analyses were performed with regard to the quality of studies (Jadad score  $\geq 3$ ), the units by which FEV<sub>1</sub> was reported in the studies (% predicted, volume [L or ml]), and specific AEs.

A pooled analysis was performed to calculate the frequency of AEs, ranked in agreement with the “European Medicine Agency, section 4.8: Undesirable effects”, as follows: very common  $\geq 1/10$ , common  $\geq 1/100$  to  $< 1/10$ , uncommon  $\geq 1/1000$  to  $< 1/100$ , frequency not known if not calculable from the available data ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2013/01/WC500137021.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/01/WC500137021.pdf)).

OpenMetaAnalyst [28] software was used for performing the meta-analysis and meta-regression, GraphPad Prism (CA, US) software to graph the data, and GRADEpro to assess the quality of evidence [15]. The statistical significance was assessed for  $P < 0.05$ , and moderate to high levels of heterogeneity were considered for  $I^2 > 50\%$ .

### 3. Results

#### 3.1. Studies characteristics

Results obtained from 820 COPD patients were selected from 20 studies [18–25,29–40] published between 1988 and 2016. The relevant studies and patients characteristics are described in Table S2. All studies were full-text papers but two that were congress abstracts [35,37]. Five studies had a Jadad score  $\geq 3$  [18,19,23,34,40], thirteen studies had a Jadad score  $\geq 1$  and  $< 3$  [20–22,24,25,29–33,36,38,39], whereas for two studies it was not possible to calculate Jadad score [35,37]. The period of treatment ranged from one day to 52 weeks.

#### 3.2. Quantitative synthesis

##### 3.2.1. Primary endpoints

Doxofylline elicited a beneficial impact on the primary endpoints of this meta-analysis. The treatment with doxofylline significantly ( $P < 0.001$ ) increased FEV<sub>1</sub> compared to control (SMD 1.14, 95%CI 0.79–1.49;  $I^2$  88%). Specifically, doxofylline induced a large to very large improvement in FEV<sub>1</sub>, in agreement with the rules of thumb for the interpretation of effect sizes on the basis of SMDs (Fig. 1) [17,26].

The subset analysis performed by assessing exclusively randomized clinical trials (RCTs) indicated that doxofylline induced a significant ( $P < 0.001$ ) increase in FEV<sub>1</sub> of 8.20% (95%CI 4.00–12.41;  $I^2$  93%) and 324 ml (95%CI 161–487;  $I^2$  91%), compared to baseline (Fig. 2A and B). A further subset analysis carried out considering exclusively the high-quality studies confirmed the relevant impact of doxofylline on FEV<sub>1</sub> (MD 239 ml, 95%CI 167–311;  $I^2$  0%;  $P < 0.001$  vs. control) (Fig. 2C).

The overall analysis of the safety profile showed that the administration of doxofylline in COPD patients induced a significant ( $P < 0.001$ ) but moderate increase of AEs frequency (Pr 0.03, 95%CI 0.02–0.04;  $I^2$  88%) (Fig. 3).

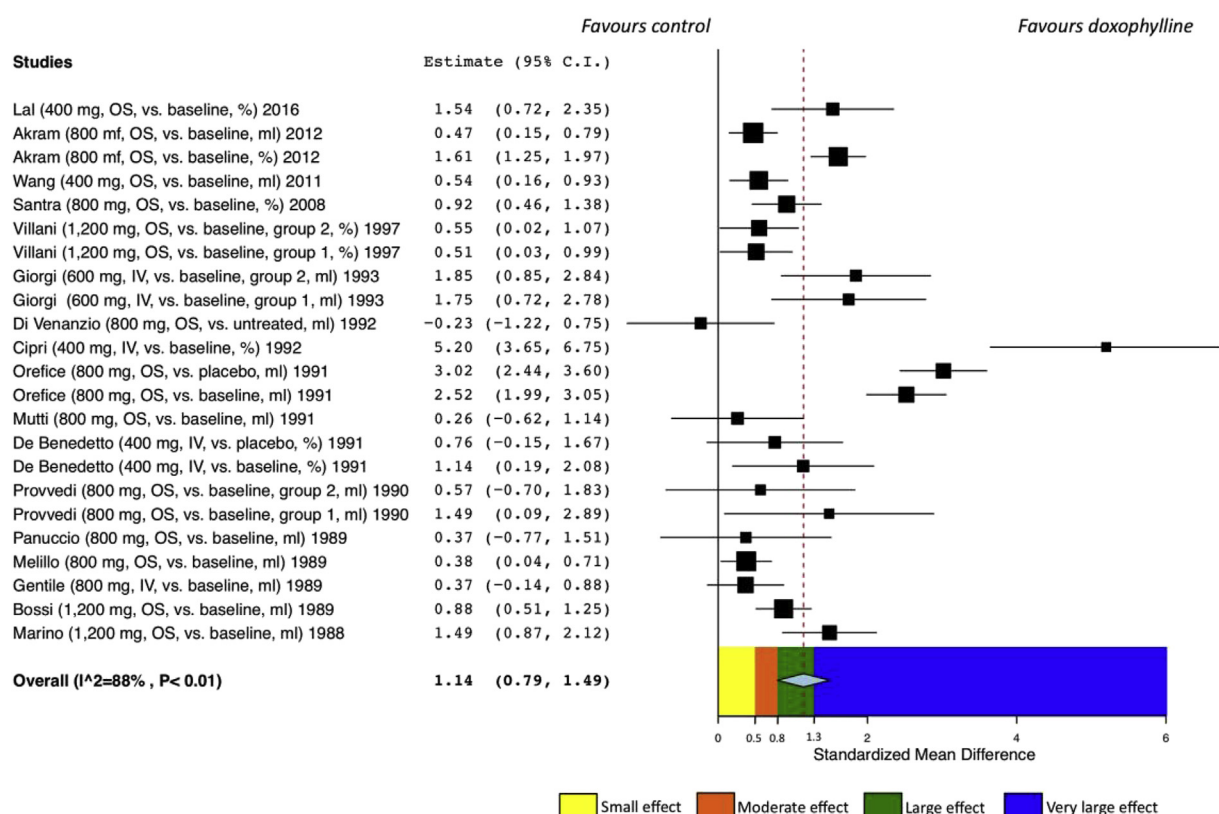
However, the subset and pooled analysis showed that among the specific AEs reported in the studies, only the frequencies of epigastralgia, nausea, dyspepsia and headache were significantly ( $P < 0.05$ ) increased in patients receiving doxofylline (Fig. 4, Table 1). Overall, 2.24% patients withdrew from the studies due to AEs.

##### 3.2.2. Secondary endpoints

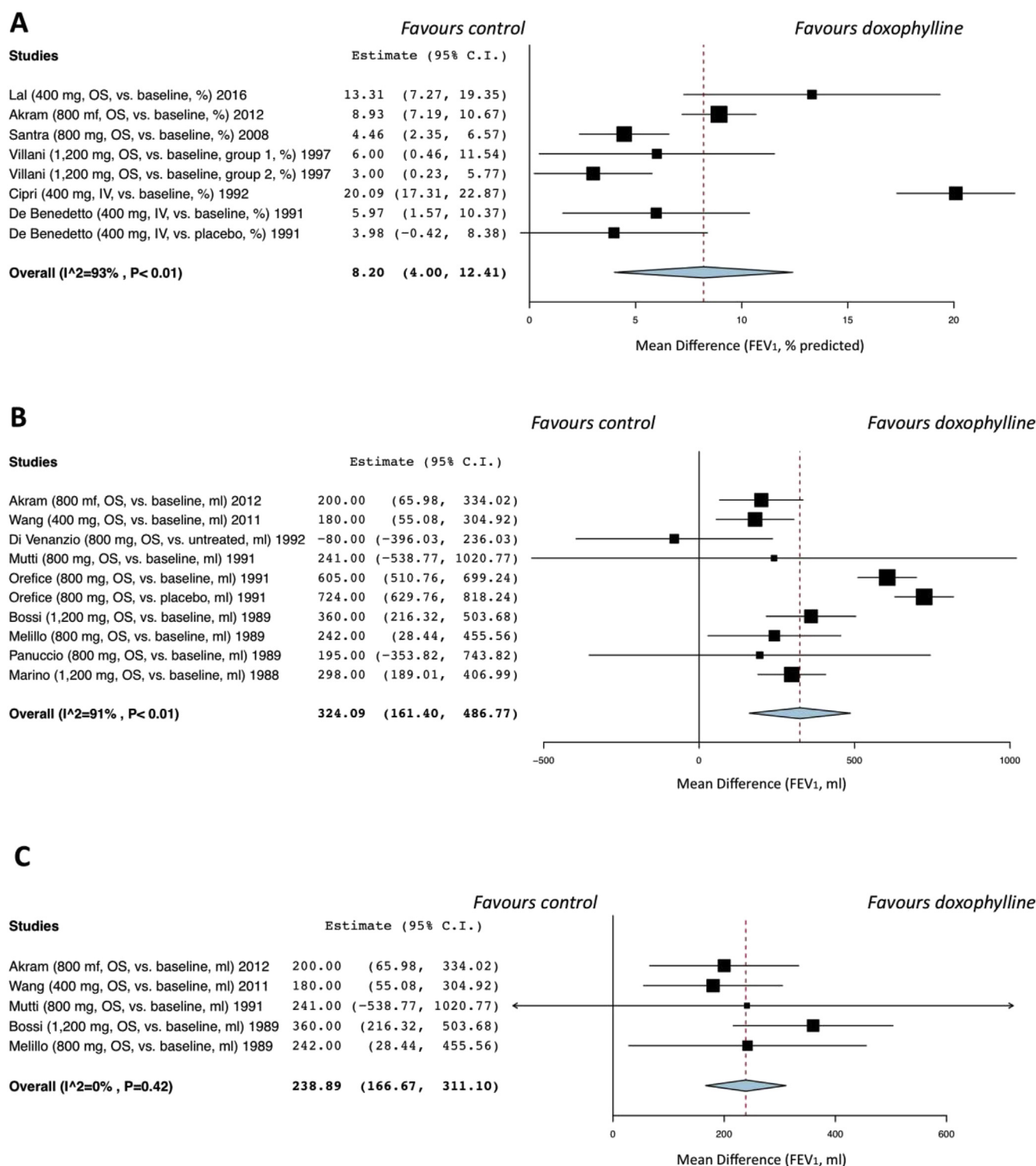
Doxofylline elicited also a beneficial impact on secondary endpoints. A significant proportion ( $P < 0.001$ ) of patients treated with doxofylline achieved a high level of therapeutic efficacy (Pr 0.82, 95%CI 0.77–0.87;  $I^2$  30%), and the daily use of rescue medication significantly ( $P < 0.001$ ) decreased more than three folds during the treatment (PLN -1.15, 95%CI -1.76 to -0.54;  $I^2$  98%). The overall improvement of dyspnea score induced by doxofylline was greater than one point (MD -1.03, 95%CI -1.09 to -0.97  $I^2$  0%;  $P < 0.001$  compared with control).

#### 3.3. Risk of bias and evidence profile

A substantial and significant ( $P < 0.001$ ) level of heterogeneity resulted in this pairwise meta-analysis concerning the primary endpoints. The sensitivity analysis indicated that the main source of heterogeneity was related to the clinical trials of Cipri et al. [24], Di Venanzio et al. [31], and Orefice et al. [36] when the analysis was focused on the impact of doxofylline on FEV<sub>1</sub>, and with the studies of Cipri et al. [24] and Wu et al. [21] when it was focused on the frequency of AEs. In



**Fig. 1.** Overall forest plot of the impact of doxofylline vs. control on the SMD in FEV<sub>1</sub> in COPD patients. The effect size of doxofylline with regard to the improvement in FEV<sub>1</sub> reported as SMD has been re-expressed in agreement with the rules of thumb proposed by Cohen and The Cochrane Collaboration<sup>®</sup> [17,26]. Specifically  $< 0.5$  represents a small effect, 0.5 to 0.8 a moderate effect, 0.8 to 1.3 a large effect, and  $> 1.3$  a very large effect. For each study the daily dose, route of administration, comparator and the method for expressing FEV<sub>1</sub> are reported. COPD: chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in 1 s; SMD: Standardized Mean Difference.



**Fig. 2.** Subgroup analysis of the impact of doxophylline vs. control on the MD in FEV<sub>1</sub> reported as % predicted (A) or volume (ml, B) by including exclusively data extracted from RCTs. Non-randomized studies and studies for which the allocation strategy was not reported have been excluded by this subset analysis. A further subset analysis (C) shows the impact of doxophylline vs. control on lung function by considering exclusively the high-quality studies characterized by a Jadad score  $\geq 3$  in which FEV<sub>1</sub> was expressed as volume (ml). For each study the daily dose, route of administration, comparator and the method for expressing FEV<sub>1</sub> are reported. FEV<sub>1</sub>: forced expiratory volume in 1 s; MD: Mean Difference; RCTs: randomized clinical trials.

fact, acceptable levels of heterogeneity were found for both the primary endpoints when these studies were excluded from the meta-analysis (FEV<sub>1</sub>:  $I^2$  42%,  $P = 0.06$ ; AEs  $I^2$  49%,  $P = 0.11$ ).

Most the meta-analyzed clinical trials enrolled stable COPD patients, but one study enrolled specifically exacerbated COPD patients [21]. Considering that the study of Wu et al. [21] reported data on the

safety profile of doxophylline but not on lung function, we assessed whether the clinical condition of COPD patients might represent a bias on the frequency of AEs. The sensitivity analysis indicated that no significant differences ( $P > 0.05$ ) were found for the effects estimates on the proportion of AEs when exacerbated COPD patients were excluded from the meta-analysis.



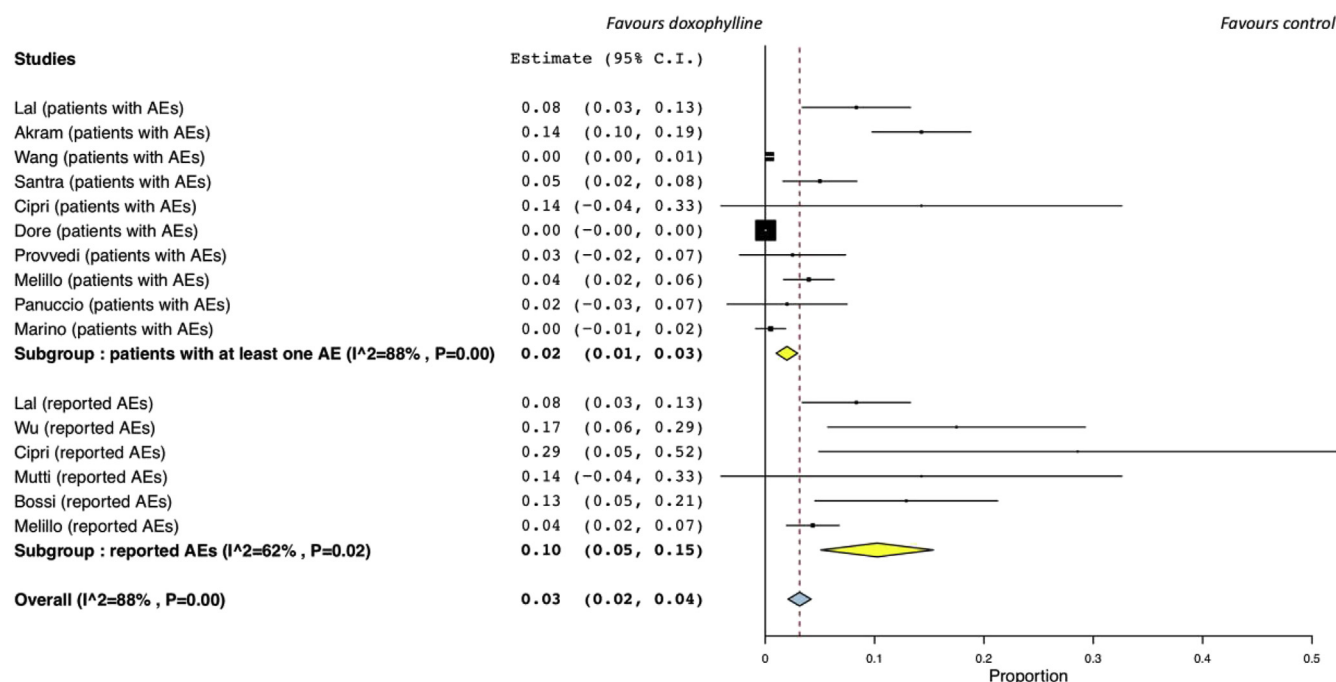


Fig. 3. Overall forest plot of the impact of doxofylline vs. control on the proportion of AEs in COPD patients. Data have been grouped in agreement with the number of patients reporting at least one AE (upper subgroup), and the total number of AEs reported in the studies included in this meta-analysis (lower subgroup). AE: adverse event; COPD: chronic obstructive pulmonary disease.

No significant heterogeneity was found either for FEV<sub>1</sub> when high quality studies were meta-analyzed ( $I^2 = 0$ ,  $P = 0.42$ ), or for the safety profile when the effect estimates of the specific AEs were considered ( $I^2 = 16$ ,  $P = 0.19$ ). Although a certain level of dispersion was detected by the visual analysis of funnel plot (Fig. 5A and C), the lack of bias concerning the effect estimates of either the primary endpoints was confirmed by Egger's test (Fig. 5B and D).

The ethnicity, the level of bronchial reversibility, and the date of publication from the first clinical trial did not represent confounder variables that may have altered the FEV<sub>1</sub> effect estimates. A signal of confounding factor was detected for the Jadad score (sub-group analysis: low quality studies SMD 1.35, 95%CI 0.84–1.13; high quality studies SMD 0.72, 95%CI 0.31–1.13) and the route of administration (sub-group analysis: intravenous SMD 1.70, 95%CI 0.67–2.74; oral SMD 1.01, 95%CI 0.63–1.39). The total dose of doxofylline administered to patients during the studies was a confounder variable for the FEV<sub>1</sub> effect estimates (sub-group analysis:  $< 30$  g SMD 0.93, 95%CI 0.62–1.24;  $\geq 30$  g SMD 2.35, 95%CI 1.51–3.19).

The ethnicity, the level of bronchial reversibility, and the date of publication from the first clinical trial and the route of administration did not represent confounder covariates with regard to the effect estimates of AEs. On the other hand, both the Jadad score (sub-group analysis: low quality studies Pr 0.35, 95%CI 0.01–0.06; high quality studies Pr 0.07, 95%CI 0.03–0.12) and the total dose of doxofylline (sub-group analysis:  $< 30$  g Pr 0.07, 95%CI 0.05–0.10;  $\geq 30$  g Pr 0.004, 95%CI 0.001–0.007) were confounder variables for the frequency of AEs.

More details on meta-regression analysis and the statistical significance of confounder variables with regard to FEV<sub>1</sub> and AEs are reported in the supplementary data file (Figure S2).

The GRADE analysis indicated high quality of evidence (++++ ) for the impact of doxofylline on FEV<sub>1</sub> expressed as volume (ml), and moderate quality of evidence (++++) for the safety profile of doxofylline administered in COPD patients (Table 2). The GRADE analysis has been carried out in high quality RCTs (Jadad score  $\geq 3$ ), excluded for FEV<sub>1</sub> expressed as % of predicted because only one high quality study [40] reported this variable.

#### 4. Discussion

The results of this pairwise meta-analysis confirm that doxofylline is effective and safe when administered to COPD patients. Compared to the control, doxofylline significantly improves lung function and dyspnea, and reduces the daily use of rescue medication more than the proposed minimal clinically important difference (MCID) values for COPD outcomes [42]. Similarly to all xanthines, it induces some AEs, but they are mild in severity. In fact, although there was a numerically larger rate of AEs in patients treated with doxofylline than in control groups, the percentage of patients that withdrew from the clinical trials due to AEs was low, and the most frequently reported ( $\geq 1\%$ ) AEs in patients receiving doxofylline were epigastralgia, nausea, dyspepsia, headache and gastrointestinal discomfort.

It is of interest that while the overall analysis of the safety profile of doxofylline in COPD showed a high level of heterogeneity, the subset analysis of the specific AEs associated with the treatment provided no significant heterogeneity of the effect estimates. In any case, the quality of evidence on the safety profile was acceptable concerning both the total number of AEs and the patients that experienced at least one AE. The findings regarding the safety profile of doxofylline contrast with the evidence that the use of theophylline at conventional doses causes a high frequency of adverse effects [43]. It is likely that the decreased affinities towards adenosine A<sub>1</sub> and A<sub>2</sub> receptors of doxofylline may account for its better safety profile [3].

It must be emphasized that doxofylline elicited a large to very large improvement in FEV<sub>1</sub>, inducing a mean improvement in FEV<sub>1</sub> of 317 ml compared to baseline values. Keeping focused exclusively on the high-quality studies, also in this case the average improvement in FEV<sub>1</sub> induced by doxofylline was large (239 ml). These values are considerably higher than those reported for theophylline in some meta-analyses [44,45]. Intriguingly, although the study of Mutti et al. [34] provided a huge level of dispersion with regard to the change in FEV<sub>1</sub> reported in ml, probably because of the low number of enrolled patients, it did not influence either the heterogeneity or the quality of evidence when the analysis was performed on high quality RCTs.

The change in percentage of FEV<sub>1</sub> (8.20% increase) is weak when

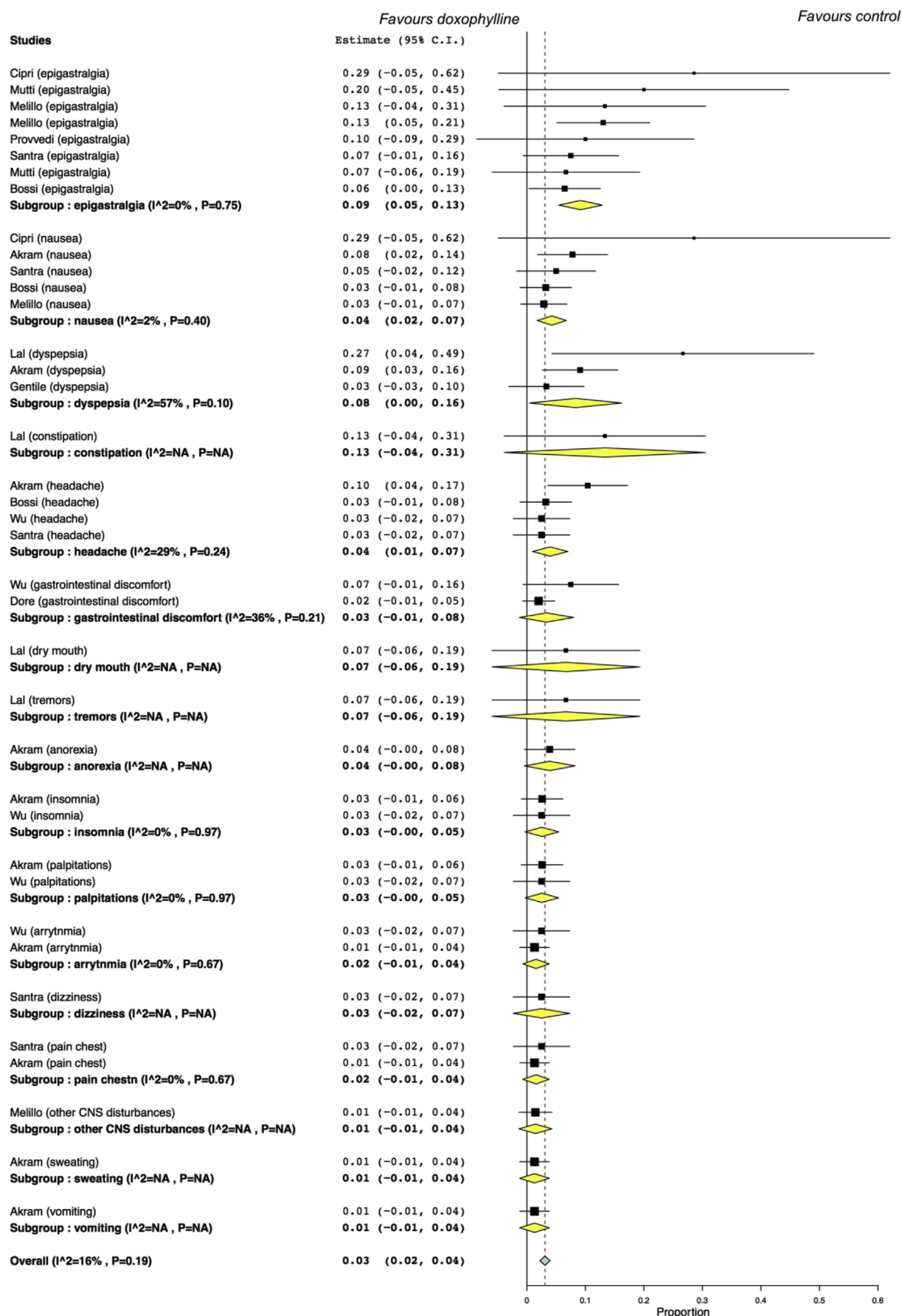


Fig. 4. Subset analysis of the impact of doxophylline vs. control on the proportion of specific AEs reported in the studies included in this meta-analysis. AEs: adverse events.

**Table 1**

Pooled analysis of AEs extracted from the studies on doxofylline in COPD patients and ranked by frequency in agreement with EMA guidelines [41].

	AEs (n)	Frequency (%)	Rank	P
Epigastralgia	21	4.28	++	***
Dyspepsia	12	2.44	++	*
Headache	12	2.44	++	*
Nausea	9	1.83	++	***
Gastrointestinal discomfort	5	1.02	++	NS
Anorexia	3	0.61	+	NS
Insomnia	3	0.61	+	NS
Palpitation	3	0.61	+	NS
Arrhythmia	2	0.41	+	NS
Constipation	2	0.41	+	NS
Dry mouth	2	0.41	+	NS
Pain chest	2	0.41	+	NS
Anxiety/irritability	1	0.20	+	NS
Dizziness	1	0.20	+	NS
Other CNS disturbances	1	0.20	+	NS
Sweating	1	0.20	+	NS
Tremors	1	0.20	+	NS
Vomiting	1	0.20	+	NS

++: common ( $\geq 1/1,00$  to  $< 1/10$ ); +: uncommon ( $\geq 1/1000$  to  $< 1/100$ );

\* $P < 0.05$  and \*\*\* $P < 0.05$ , in agreement with the proportion of specific AEs reported in the studies included in this meta-analysis; AEs: adverse events; COPD: chronic obstructive pulmonary disease; EMA: European Medicine Agency; NS: not significant.

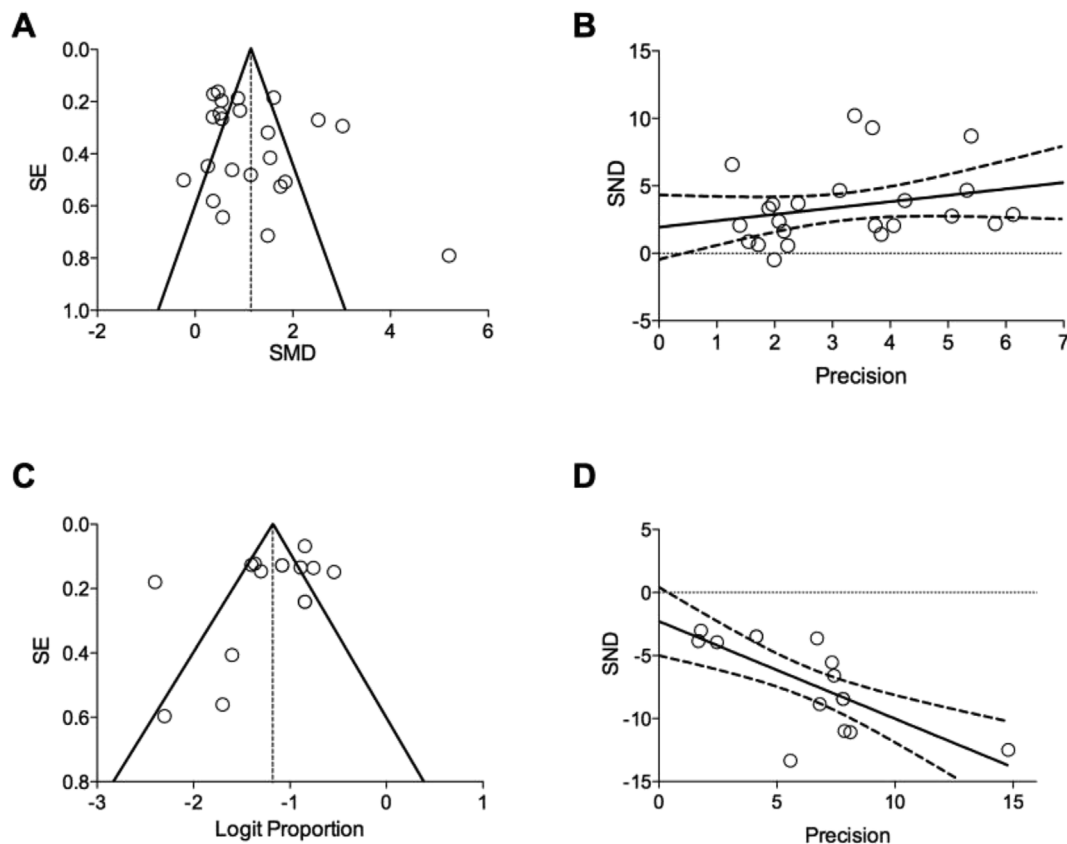
compared with the change reported in ml. Such a discrepancy can be explained by considering that all the high quality RCTs expressed the changes in FEV<sub>1</sub> as volume and that the GRADE analysis provided a high quality of evidence for this outcome. Conversely, the studies that reported the impact of doxofylline on the percentage of change in FEV<sub>1</sub>

were low quality studies that provided just low quality of evidence.

This meta-analysis has certainly some limitations that need to be highlighted. It has been impossible to evaluate the effect of doxofylline taking into account the severity of the disease and clinical condition of COPD patients, the presence of comorbidities, and use of concomitant medications. Furthermore, most clinical trials did not use a placebo as comparator. There was also a wide range of drug exposure between the studies analyzed, from hours to days or even months. In fact, the meta-regression analysis, a tool that permits to quantify the impact of moderator variables on study effect size [46], has shown that the total dose of doxofylline administered to patients during the studies has influenced the change in FEV<sub>1</sub>. In any case, our analysis does not allow us to conclude that a longer-term treatment is better than a shorter-term treatment regimen or that higher doses are necessary for increased severity of the COPD. Nonetheless, the evidence generated by the meta-regression analysis that a longer treatment time leads to less AEs seems to be very interesting and maybe suggest that tolerance to AEs may be possible following chronic treatment with doxofylline.

The limitations of this study mainly stem from the lack of specific information in the papers that are being considered and, consequently, cannot be overcome by further analysis. Thus, the overall results of this quantitative synthesis should be interpreted with caution.

However we must point out that, when high quality RCTs were meta-analyzed, the quality of evidence was high for the impact of doxofylline on the change in FEV<sub>1</sub> expressed as volume (ml), and acceptable with regard to the influence of doxofylline on the frequency of AEs. The quality of the effect estimates resulting from the analysis of high quality RCTs was also confirmed by the visual analysis of funnel plot, a graphical method to check for the existence of publication bias, and supported by Egger's test, which assesses whether the funnel plot is symmetrical by measuring the intercept from regression of standard



**Fig. 5.** Funnel plot (left panels) and graphical representation of Egger's test (right panels) for the overall impact of doxofylline vs. control on the changes in FEV<sub>1</sub> (A and B) and the frequency of AEs (C and D). AEs: adverse events; FEV<sub>1</sub>: forced expiratory volume in 1 s; SE: standard error; SMD: standardized mean difference; SND: standard normal deviate.



**Table 2**GRADE evidence profile: impact of doxofylline vs. control (placebo, untreated subjects, baseline values) on changes in FEV<sub>1</sub> and frequency of AEs in COPD patients.

Outcome	Quality assessment: impact of doxofylline in COPD				Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	
FEV <sub>1</sub> (ml) from high quality RCTs	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
FEV <sub>1</sub> (% predicted) from all RCTs	Serious <sup>a</sup>	Serious <sup>b</sup>	Not serious	Not serious	⊕⊕○○ Low
AEs (patients with at least one AE) from high quality RCTs	Not serious	Serious <sup>b</sup>	Not serious	Not serious	⊕⊕⊕○ Moderate
AEs (reported AEs) from high quality RCTs	Not serious	Serious <sup>b</sup>	Not serious	Not serious	⊕⊕⊕○ Moderate

**GRADE Working Group grades of evidence**  
**High quality:** we are very confident that the true effect lies close to that of the estimate of the effect.  
**Moderate quality:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
**Low quality:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.  
**Very low quality:** we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect.

<sup>a</sup> Confirmed by Jadad score.<sup>b</sup> Confirmed by I<sup>2</sup>; AEs: adverse events; FEV<sub>1</sub>: forced expiratory volume in 1 s; RCTs: randomized clinical trials.

normal deviates against precision [47].

## 5. Conclusions

Notwithstanding the above-mentioned limitations, this pairwise meta-analysis suggests that in patients with COPD doxofylline acts as a bronchodilator drug having a wider therapeutic window than theophylline. These characteristics, along with its well-described anti-inflammatory [48] and steroid sparing effects [49] suggest that when a xanthine is indicated [50], doxofylline should be considered as an alternative to theophylline in the treatment of patients with COPD.

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## Declaration of interest

MC and MGM are consultants at the ABC Farmaceutici and CP at Eurodrug that manufacture and sell medicinal products containing doxofylline. LC received compensation for working on this manuscript. PR has no competing interests.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.pupt.2018.04.010>.

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